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(54) Title: USE OF GRISEOFULVIN FOR INHIBITING THE GROWTH OF CANCERS

(57) Abstract

A pharmaceutical composition for the treatment of cancers or tumors in mammals is disclosed which comprises griseofulvin. A chemotherapeutic agent can be used in conjunction with griseofulvin as can potentiators. Griseofulvin can also be used to treat viral infections, either alone, in conjunction with other viral agents or with a potentiator.

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Use of griseofulvin for inhibiting the growth of cancers

TECHNICAL FIELD

This invention is a pharmaceutical composition that is useful for the treatment of cancers and tumors, particularly in human and warm blooded animals. The composition contains griseofulvin. It can be used in combination with other chemotherapeutic agents also.

BACKGROUND OF THE INVENTION

Cancers, including leukemia, are the leading cause of death in animals and humans. The exact cause of leukemia is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of leukemia and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against cancers, tumors and leukemia, but not all types of cancer and tumor cells respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

Despite advances in the field of cancer and leukemia treatments the leading therapies to date are radiation and chemotherapy and bone marrow transplants. Chemotherapeutic approaches are said to fight cancers that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for leukemia, cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both diseased and normal) have been used.

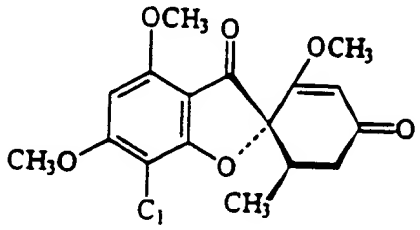
Clearly, the development of materials that would target cancer or leukemia cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to leukemia or cancer cells while exerting mild effects on normal cells would be desirable. Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in treating leukemia with mild or no effects on normal blood cells

More specifically, it is an object of this invention to provide a composition comprising a pharmaceutical carrier and a griseofulvin as defined herein along with a method for treating cancer, leukemia and tumors.

The use of griseofulvin in combination with other chemotherapeutic agents which are effective in destroying the tumor is a novel method of treatment. Griseofulvin can also be used to treat viral infections in the presence of a potentiator.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, which are affected by leukemia comprising a pharmaceutical carrier and an effective amount of griseofulvin. Griseofulvin has the formula:



These compositions can be used to inhibit the growth of leukemia, tumors and cancer cells in humans or animals by administration of an effective amount either orally, rectally, topically or parenterally, or intravenously. These compositions do not significantly affect healthy cells.

Potentiators can also be used in combination with griseofulvin as can chemotherapeutic agents.

DETAILED DESCRIPTION OF THE INVENTION

A. DEFINITIONS:

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the durati n of the treatment, the nature of concurrent

therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" is salt of the anti-leukemia compound with an organic or inorganic acid. These preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-leukemia agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" or "leukemia" refers to all types of cancers or neoplasm or malignant disease which attack normal healthy blood cells or bone marrow which produces blood cells which are found in mammals.

As used herein, "viruses" includes viruses which cause diseases in warm blooded animals including HIV, influenza, rhinoviruses, herpes and the like.

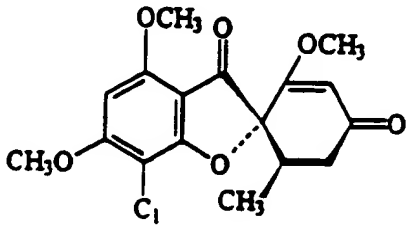
As used herein, "griseofulvin" means 7-Chloro-2',4,6-trimethoxy-6-methylspiro [benzofuran-2-(3H),1'-[2]cyclohexene]-3,4'-dione. It is an antibiotic substance produced by *penicillium griseofulvum*

As used herein "potentiators" are materials such as triprolidine and its cis-isomer which are used in combination with griseofulvin. Potentiators can suppress the immune system or enhance the effectiveness of the drugs.

As used herein "chemotherapeutic agents" includes DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others, such as Asparaginase or hydroxyurea.

B. GRISEOFULVIN

Griseofulvin has the following structure:



It is prepared according to the method described in U.S. 3,069,328 issued to Hockenhull (1962) and U.S. 3,069,328 issued to Dorey et al. (1962)

C. CHEMOTHERAPEUTIC AGENTS

The chemotherapeutic agents are generally grouped as DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others such as Asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in combination with griseofulvin include members of all of these groups. For a detailed discussion of the chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook*, 2d edition, pages 15-34, Appleton & Lange (Connecticut, 1994) herein incorporated by reference.

DNA-Interactive Agents include the alkylating agents, e.g. Cisplatin, Cyclophosphamide, Altretamine; the DNA strand-breakage agents, such as Bleomycin; the intercalating topoisomerase II inhibitors, e.g., Dactinomycin and Doxorubicin); the nonintercalating topoisomerase II inhibitors such as, Etoposide and Teniposde; and the DNA minor groove binder Plicamydin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include:

Nitrogen mustards, such as Chlorambucil, Cyclophosphamide, Isofamide, Mechlorethamine, Melphalan, Uracil mustard;

Aziridine such as Thiotepa

methanesulphonate esters such as Busulfan;

nitroso ureas, such as Carmustine, Lomustine, Streptozocin;

platinum complexes, such as Cisplatin, Carboplatin;

bioreductive alkylator, such as Mitomycin, and Procarbazine, Dacarbazine and Altretamine;

DNA strand breaking agents include Bleomycin;

DNA topoisomerase II inhibitors include the following:

Intercalators, such as Amsacrine, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone;

nonintercalators, such as Etoposide and Teniposide.

The DNA minor groove binder is Plicamycin.

The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replicati n. Some of the compounds are sufficiently like purines or pyrimidines to be able to

substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include:

folate antagonists such as Methotrexate and trimetrexate

pyrimidine antagonists, such as Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, and Floxuridine

purine antagonists include Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin;

sugar modified analogs include Cyctrabine, Fludarabine;

ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin Interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell can not form microtubules Tubulin Interactive agents include Vincristine and Vinblastine, both alkaloids and Paclitaxel.

Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include:

estrogens, conjugated estrogens and Ethinyl Estradiol and Diethylstilbesterol, Chlortrianisen and Idenestrol;

progestins such as Hydroxyprogesterone caproate, Medroxyprogesterone, and Megestrol;

androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone;

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, Prednisone, Dexamethasone, Methylprednisolone, and Prednisolone.

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include:

antiestrogenic agents such as Tamosifen,

antiandrogen agents such as Flutamide ; and

antiadrenal agents such as Mitotane and Aminoglutethimide.

Hydroxyurea appears to act primarily through inhibition of the enzyme ribonucleotide reductase.

Asparaginase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor.

D. POTENTIATORS

The "potentiators" can be any material which improves or increase the efficacy of the pharmaceutical composition or acts as an immunosuppressor. One such potentiator is triprolidine and its cis-isomer which are used in combination with the chemotherapeutic agents and the griseofulvin. Triprolidine is described in US 5,114,951 (1992). Another potentiator is procodazole, 1H-Benzimidazole-2-propanoic acid; [ß-(2-benzimidazole) propionic acid; 2-(2-carboxyethyl)benzimidazole; propazol]. Procodazole is a non-specific active immunoprotective agent against viral and bacterial infections and can be used with the compositions claimed herein. It is effective with griseofulvin alone in treating cancers, tumors, leukemia and viral infections or combined with chemotherapeutic agents.

Propionic acid and its salts and esters can also be used in combination with the pharmaceutical compositions claimed herein.

Antioxidant vitamins such as vitamins A, C and E and beta-carotene can be added to these compositions.

E. DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and the type of cancer or tumor or viral infection being treated. Generally a dosage of between about 1 milligram (mg) per kilogram (kg) of body weight and about 8000 mg per kg of body weight is suitable for either the griseofulvin or the chemotherapeutic agent. Preferably from 15 mg to about 5000 mg/kg of body weight is used. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The dosage unit can also comprise diluents, extenders, carriers, liposomes and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral, rectal, topical, intravenous injection or parenteral administration or injection into or around the bone marrow. The range and ratio of griseofulvin to chemotherapeutic agent will depend on the type of cancer or tumor being treated and the particular chemotherapeutic agent.

F. DOSAGE DELIVERY FORMS

The chemotherapeutic agents, griseofulvin and, optionally, the potentiators are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid

forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

G. METHOD OF TREATMENT

The method of treatment can be any suitable method which is effective in the treatment of the particular cancer or tumor type being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the tumor or cancer. The method of applying an effective amount also varies depending on the leukemia, cancer, tumor or virus being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application of the griseofulvin, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

In addition to the use of chemotherapeutic agents and potentiators, griseofulvin can be combined with fungicides, herbicides or other antiviral agents. Preferred herbicides and fungicides include carbendazim, fluoconazole, benomyl, glyphosate and propicodazole.

Example 1

In an acute HIV in vitro model, griseofulvin inhibited viral replication by 98% at 10μg/ml with a therapeutic index of 5.3. AZT, a known HIV drug, also inhibited viral replication by 98% at 1μg/ml with a therapeutic index of 12,500. The therapeutic index is the ratio of toxic dose of drug to efficacious dose of drug.

Example 2

In an in vivo mouse study for leukemia (P388), griseofulvin showed an increase in the survival time relative to a non treated control of 156% at 4000 mg/kg dose; 188% at 5000 mg/kg dose; and 218% at 6000 mg/kg dose.

Example 3

In an in vivo mouse study for melanoma (B16), griseofulvin showed an increase in the survival time relative to a nontreated control of 165% at 4000 mg/kg dose; 179% at 5000 mg/kg dose; and 201% at 6000 mg/kg dose. Cytoxan at 300 mg/kg showed an increased survival rate of 192%.

Example 4

In an in vitro screening for Rhinovirus, type A-1, cell line WI-38, griseofulvin was effective at 100 µg/ml. The positive control was A-36683 of Abbot Company, (S,S)-1,2-bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol. A-36683 has a therapeutic index of 1000-3200. Griseofulvin has a therapeutic index of 1-2. (See Schleicher et al, *Applied Microbiology*, 23, No. 1, 113-116 (1972).

Example 5

Solid tumors removed by patients are minced into 2 to 5 mm fragments and immediately placed in McCoy's Medium 5A plus 10% heat inactivated newborn calf serum plus 1% penicillin/streptomycin. Within 4 hours, these solid tumors are mechanically disassociated with scissors, forced through No. 100 stainless steel mesh, through 25 gauge needles, and then washed with McCoy's medium as described above. Ascitic, pleural, pericardial fluids and bone marrow are obtained by standard techniques. The fluid or marrow is placed in sterile containers containing 10 units of preservative free heparin per ml. of malignant fluid or marrow. After centrifugation at 150 x g for 10 minutes, the cells are harvested and washed with McCoy's medium plus 10% heat inactivated calf serum. The viability of cell suspensions is determined on a hemocytometer with trypan blue.

Cells to be cloned are suspended in 0.3% agar in enriched CMRL1066 supplemented with 15% heat inactivated horse serum, penicillin (100 units/ml), streptomycin (2mg/ml), glutamine (2mM), insulin (3 units/ml), asparagine (0.6 mg/ml), and HEPES buffer (2mM). For the continuous exposure test each compound is added to the above mixture. Cells are placed in 35 mm petri dishes in a top layer of agar over an underlayer of agar to prevent growth of fibroblasts. Three plates are prepared for each data point. The plates are placed in a 37°C incubator, and are removed on day 14 for counting of the number of colonies in each plate. The number of colonies (defined as 50 cells) formed in the 3 compound treated plates is compared to the number of colonies formed in the 3 control plates, and the percent colonies surviving at the concentration of compound can be estimated. Three positive control plates are used to determine survival rate.

Orthosodium vanadate at 200 µg/ml is used as the positive control. If there is <30% colonies in the positive control when compared to the untreated control, the test is evaluated.

At concentration of 0.5 and 5.0 µg/ml in a single dose experiment griseofulvin was not effective (0/1) against tumors in this test. At concentration of 50.0 µg/ml in a continuous exposure experiment griseofulvin was effective against colon, lung, non-small cell, and ovarian cancers . Over all 5 of 6 had ≤50% survival.

1. A pharmaceutical composition for treating cancer and tumors comprising a pharmaceutical carrier and from 1 mg/kg to about 8000 mg/kg per body weight.

2. A pharmaceutical composition according to Claim 1 comprising a potentiator.

3. A pharmaceutical composition according to claim 1 and 2 comprising a pharmaceutically acceptable carrier and a safe and effective amount of griseofulvin and a chemotherapeutic agent.

4. A pharmaceutical composition according to claim 1,2 or 3 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents, Asparaginase or hydroxyurea.

5. A pharmaceutical composition according to claim 1, 2 or 4 wherein said chemotherapeutic agent is selected from the group consisting of Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide and Plcamydin.

6. A pharmaceutical composition according to claim 1, 2 or 4 wherein said chemotherapeutic agent is selected from the group consisting of Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin, Cyctrabine, and Fludarabine.

7. A method of treating cancer or tumors in warm blooded mammals comprising administering a composition according to claims 1, 2, 3, 4, 5 or 6.

8. A method of treating viral infections in warm blooded mammals comprising administering a composition according to claims 1, 2, 3, 4, 5, or 6.

9. A unit dosage composition for treating viral infections in animals or humans comprising a pharmaceutical carrier and from 1 mg/kg to about 8000 mg/kg of body weight.

10. A unit dosage composition for treating cancer or tumors in animals or humans comprising a pharmaceutical carrier and from 1 mg/kg to about 8000 mg/kg of body weight.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
THE PROCTER & GAMBLE COMPANY
Attn. REED, T. David
5299 Spring Grove Avenue
Cincinnati, Ohio 45217
UNITED STATES OF AMERICA

cc: Watty / EC atty / AA / file
R.A. Dabek V. Woof / Egham
Att - Note title change

CL 1354/96 ZA (John)

Applicant's or agent's file reference 5784/AA	Date of mailing (day/month/year) 20/02/1997
International application No. PCT/US 96/ 12475	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant THE PROCTER & GAMBLE COMPANY	International filing date (day/month/year) 30/07/1996

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Maria Van der Hoeven

Form PCT/ISA/220 (January 1994)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Noufication of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
5784/AA		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 96/ 12475	30/07/1996	03/08/1995
Applicant		
THE PROCTER & GAMBLE COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] Certain claims were found unsearchable (see Box I).

2. [ ] Unity of invention is lacking (see Box II).

3. [ ] The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

   [ ] filed with the international application.

   [ ] furnished by the applicant separately from the international application,

      [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

   [ ] Transcribed by this Authority

4. With regard to the title,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   USE OF GRISEOFULVIN FOR INHIBITING THE GROWTH OF CANCERS

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/12475

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THERAPIE, vol. 22, no. 5, 1967, pages 1143-1151, XP000617126 E. HUANT: "Premières expérimentations cliniques de l'activité anti-mitotique de la griséofulvine en thérapeutique antitumorale." see the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 1997	20.02.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Orviz Diaz, P

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